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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,422	02/28/2005	Tomohiro Tsuji	Q85108	4344

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EXAMINER	
WOOD, AMANDA P	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,422	TSUJI ET AL.	
	Examiner	Art Unit	
	Amanda P. Wood	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04, 7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Claims 1-10 in the reply filed on 20 March 2007 is acknowledged.

Claims 1-10 are presented for consideration on the merits.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 6-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 11650962. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claims of the

instant application teach and use a reagent for the purpose of differentiating immature leukocytes in a sample from other cells by damaging the cell membrane of red blood cells and mature leukocytes and then staining the nucleic acid of mature leukocytes, which would render obvious the reagent and reagent kit of the cited Application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakata et al (EP 0844481) A1) in view of Thompson et al (US 2001/0049091 A1) and Mizukami et al (6,004,816).

A method of classifying and counting leukocytes comprising a step of staining cells obtained from a hematological sample treated with a hemolytic agent, a step of measuring the scattered light and fluorescence of the cells in a flow cytometer, and a step of classifying and counting leukocytes based upon a difference in the intensity of a scattered light peak and a difference in the scattered light width, is claimed.

Sakata et al beneficially teach a method wherein a hematological sample is treated with a hemolytic agent that maintains immature leukocytes in a viable state

without damage but damages other leukocytes. Sakata et al teach that by damaging the leukocytes with hemolytic agent the cells are permeable to the fluorescent dye used to stain the cells' DNA, therefore only cells that have were damaged by the hemolytic agent will stain and the intensity of the fluorescent staining will correspond to the amount of DNA present in the cells, while the scattered light indicates cell size. Sakata et al beneficially teaches that the hemolytic agent used in the method comprises surface-active agents, including polyoxyethylene-based nonionic surfactants of the formula represented on page 3, solubilizers of the formulas on pages 3-4, and other ingredients as shown on page 7. Sakata et al further teach that the dye used to stain the permeabilized leukocytes is preferably a dye with specificity for the cell nucleus, especially for DNA, and in particular, cationic dyes are preferred, including those dyes listed on pages 4 and 5 (see, for example, the dye of formula I, page 5). Sakata et al teach a method wherein a flow cytometer is used to measure the sample containing stained leukocytes by measuring the scattered light and fluorescence of the cells. Sakata et al further teach a method wherein leukocytes are classified and counted based upon scattered light and fluorescence in combination. Sakata et al beneficially teach a method wherein at least one type of side scattered light and forward scattered (low or high angle) light are measured, and furthermore, Sakata et al teach in Figure 1 that both forward and side scattered light can be measured at the same time, providing the functional equivalent of measuring the scattered light peak and scattered light width. In addition, Sakata et al beneficially teach a method wherein mature and immature leukocytes are classified into at least three groups and two groups, respectively, using

the difference in scattered light intensity and the difference in the fluorescence intensity measured in the sample. Sakata et al further teach in Figure 2 that the ratio of immature granulocytes (i.e., immature leukocytes) relative to mature leukocytes can be determined from the instant method, wherein Fig. 2A indicates that immature granulocytes make up 3.5% of the population of leukocytes in the sample, and Fig. 2B indicates that immature granulocytes make up 7.5% of the population of leukocytes in the sample, and blasts represent another 2% of cells in the sample (see, for example, Abstract, pg. 2, lines 30-57; pg. 3, lines 5-55; pg. 4, lines 1-55; and pg. 7, lines 35-57).

Sakata et al does not expressly teach a method wherein leukocytes with an abnormal DNA amount are counted and classified using a method comprising fluorescent staining and measurement of the stained cells with a flow cytometer.

Thompson et al beneficially teach a method wherein the ploidy (i.e., measure of the amount of DNA contained in a cell) of cells is tested and compared to non-cancerous cells, wherein if the ploidy of the test cell is greater than that of a non-cancerous cell, then it indicates a probability that the test cell is more likely to be cancerous. Thompson et al beneficially teach that the test for ploidy can be performed on test cells derived from human blood, as well as other biological samples. In addition, Thompson et al beneficially teach that intercalating agents which bind to DNA to produce a fluorescent product are preferred to use, and that flow cytometry has been used to determine ploidy using fluorescence. Thompson et al teach that to stain cells with intercalating agents, the cell membrane must be permeabilized by exposing the cell to a detergent so that the dye can interact with chromosomal DNA to produce the

fluorescent product. Thompson et al beneficially teach that the cells are then placed into a cell sorter under conditions for the dye to fluoresce, wherein the signal is detected and quantified. Furthermore, Thompson et al teach that cancerous and non-cancerous cells are treated in the same way to determine typical ploidies of the cells and then a comparison is made between the fluorescent intensity of test cells with that of cancer and non-cancer cells. Thompson et al beneficially teach that cancerous cells typically have a higher fluorescence due to higher ploidy than non-cancerous cells (see, for example, pg. 4, pgh. 39-40; pg. 5, pgh. 41; pg. 8, pgh. 121-127).

Mizukami et al beneficially teach a method wherein using one or more types of scattered light in flow cytometry measurements can increase the precision of classification. In particular, Mizukami et al teach that forward low-angle scattered light gives information on the sizes of cells, whereas the use of forward high-angle scattered light gives information that is intermediate between the information obtained using forward low-angle scattered light and that obtained using lateral scattered light (i.e., information including the cellular size information and the cellular internal structure information is obtained). Therefore, Mizukami et al beneficially teach that cells can be classified into at least two groups based on the difference in the forward low angle scattered light in the Y-axis (i.e., the intensity of a scattered light peak) and a difference in the lateral scattered light in the X-axis (i.e., the intensity of a scattered light width), therefore, making it possible to separate cells based upon size and intracellular properties (see, for example, Fig. 3, and col. 6).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed by Sakata et al based upon the beneficial teachings provided by Thompson et al, with respect to the art-recognized method of permeabilizing cells for the purpose of staining and quantifying the cell's DNA so as to differentiate between cells with normal amounts of DNA and those with abnormal amounts of DNA, such as would be likely to occur in cancerous cells, as discussed above. In addition, it would have been obvious to modify the teachings of Sakata et al based upon the beneficial teachings provided by Mizukami et al, with respect to the art-recognized fact that using more than one type of scattered light in flow cytometry measurements increases the precision of classification of cells present in the sample by providing more information about the sizes of cells present and the intracellular structure. Mizukami et al beneficially teach that providing more information about the size and intracellular structure of cells present enables one to more clearly identify cells by where they fall on a scattergram, as in Fig. 3, and therefore, it would have been both obvious and beneficial for one of ordinary skill in the art at the time the present invention was made to use the same technique to determine whether cells could be classified as leukocytes or as platelets, erythrocyte ghosts, etc. that may be in the sample so as to differentiate between cells that show up on the scattergram for the express purpose of clearly identifying only the cells of interest during measurements. Sakata et al beneficially teach a method for staining leukocytes using a hemolytic agent to permeabilize the cells and a fluorescent dye to stain the cells prior to measurement with a flow cytometer. Furthermore, Thompson et al particularly point out

that cancerous cells tend to have higher ploidy than non-cancerous cells, and therefore have more DNA, and that staining with fluorescent stain and subsequent measurement with flow cytometry is useful in determining the ploidy, and therefore, quantity of DNA in cells, e.g., in cells derived from blood to differentiate amongst cells to determine their ploidy, and therefore, it would have been obvious and beneficial for the skilled artisan to use the methods taught by Sakata et al, Thompson et al, and Mizukami et al so as to classify and count leukocytes by differentiating between immature leukocytes, mature leukocytes, and leukocytes with an abnormal amount of DNA. The result-effective adjustment of particular conventional working conditions (e.g., using particular scattered light measurements for classifying cells) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole, was *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made, as evidenced by the cited references, especially in the absence of evidence to the contrary.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Oelschlaegel et al (J. Immun. Methods 2001) is made of record, but not relied upon as prior art. Oelschlaegel et al teaches substantially the same methods as that of Thompson et al cited above.

Mizukami et al (cited above) is considered pertinent to Applicant's disclosure with regard to the reagent and method for classification and counting of leukocytes. The dye reagent taught by Mizukami et al differs from that used in Applicant's method, wherein Mizukami et al's reagent specifically binds RNA, Applicant's method calls for a dye which can make a difference in the fluorescence intensity between mature leukocytes and leukocytes with an abnormal DNA amount, a property not shared by Mizukami et al's reagent. Furthermore, the dye reagent taught by Mizukami et al differs from that taught by Applicants in the attachment of the R4 group to the ring structure. In addition, Applicant specifically teaches several alternative dyes which can be used to stain leukocytes, examples which are not taught or claimed by Mizukami et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business

Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

APW
Examiner
Art Unit 1657

APW

CHRISTOPHER R. TATE
PRIMARY EXAMINER